PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X-14688		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 02/21297	29.07.2002	17.01.2002

International Patent Classification (IPC) or both national classification and IPC
C07D401/12, C07D401/12

Applicant
ELI LILLY AND COMPANY

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.01.2003	24.03.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 02/21297

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-85 as originally filed

Claims, Numbers

1-57 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-7(industrial applicability),8-17,36(part)-45(part), 53(part)-57(part)

because:

☒ the said international application, or the said claims Nos. 1-7 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 8-17,36(part)-45(part), 53(part) -57(part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	6,7,20,22-52
	No: Claims	1-5,18,19,21,53-57
Inventive step (IS)	Yes: Claims	
	No: Claims	1-7, 18-57
Industrial applicability (IA)	Yes: Claims	18-57
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Claims 1-7 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

2- This preliminary examination is limited to the parts of the application for which the international search report has been established, namely the subject matter of claims 1 to 7 and the parts of claims 18 to 57 relating to the compounds of formula (II) and the compounds defined in claims 46 and 49 (Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents cited in the search report:

d1: WO 01 51469 A
d2: US-A-6 124 323
d3: US-A-4 705 853
d4: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, retrieved from STN, accession no. 2001: 425735 Database accession no. 136:247481

2- The present application does not comply with the requirements of Art 33.2 PCT. Present claims 1 to 7 relate to a method of treatment of the conditions "indicating treatment with a beta 4 subtype selective nicotinic acetylcholine modulator". From the description (pages 2 and 43-44) it is understood that said conditions include Parkinson disease, Alzheimer disease, dementia, cognitive disorders and neurodegenerative disorders.
D1 discloses a class of piperidine or piperazine derivatives which overlaps with present compounds of formula (I). Some compounds of d1, such as for instance the first two compounds of example 1 are included in the formula (I) of present claim 1 (taking into account of the definition of the group "aryl" (R1) which includes also substituted aryl derivatives). The compounds of d1 are used for the treatment of various neurological disorders including Alzheimer and Parkinson diseases.

Accordingly, d1 discloses the use of compounds partly identical to present compounds of formula (I) for the same methods of treatment.
D1 appears to anticipate the subject matter of present claims 1 to 5.
D1 discloses also many compounds included in the scope of present formula (II) but excluded for the effect of the disclaimer (see in particular the compounds of example 2).
The compounds disclosed in d4 having Registry Numbers 403848-69-1 and 403848-67-9 appear to fall in the ambit of present claims 18,19,21,53-57. There is no evidence form d4, that these compounds have the same therapeutic use of present compounds. Thus, claims 1 to 7 are novel vis-à-vis d4.

The general formula (I) of d2 overlaps with present formula (I) when X (in d2) is S and Y is a bond. However, d4 does not disclose any single compound having both these features. Thus, present compounds and their uses are regarded as novel in respect of d2.
The compound disclosed in the Preparation 22 of d3 seems to be excluded from the scope of present claim 18 by effect of the disclaimers. The compounds of d3 do not have the same activity of present compounds.

In view of the above considerations, it is considered that claims 1-5, 18,19,21,53-57 do not meet the requirement of novelty.

3.1- The applicant seems to have set himself the task of providing partly-novel agents capable to modulate the beta 4 subtype nicotine acetylcholine receptor and useful for the treatment of various disorders including Alzheimer disease, dementia, cognitive disorders and neurodegenerative disorders.
Documents d1 and d2 relate to compounds having the same therapeutic use of present compounds. Considering the chemical structures of the compounds disclosed, it is considered that d1 represent the closest state of the art.
The technical problem may be seen in the provision of novel and known agents for the treatment of various neurological disorders such as those defined above.

3.2- D1 already discloses compounds which are similar or identical to the compounds of the invention and possess the same therapeutic activity. In addition, also d2 describes a family of compounds, used inter alia for the treatment of neurodegenerative disorders, which partly includes present compounds of formula (I).
Considering this state of the art, it appears that the contribution provided by the present invention does not involve any inventive skill because it was already know to use

compounds similar or identical ot the present compounds for solving the above-defined technical problem.

3.3- The specific biochemical activity of the present compounds as modulators of the beta 4 subtype receptor, has been considered. However, it is considered that the modulation of a receptor cannot be regarded *per se* as a technical effect having a practical application in the absence of the definition of the pathological conditions that can be treated by the modulation of this receptor.
The modulation of a specific receptor could be regarded as a relevant factor for the acknowledgment of the inventive activity only in the presence of instructions, available from the state of the art, allowing the skilled person to recognise which are the conditions that can be treated by the modulation of this receptor and provided that the skilled person would not consider obvious to use the same compounds for the treatment of these conditions.